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Innate immunity as a driving force in renal disease

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Mrug *et al.* propose that innate immunity is a hallmark of progressive polycystic kidney disease (PKD). We propose that innate immunity is a driving force in the progression of many renal diseases. Renal epithelial cells are capable of expressing a large variety of proinflammatory genes resulting in the production of cytokines, chemokines, cell-adhesion molecules, and complement components. We suggest that future therapeutic interventions should be directed toward control of innate immunity in renal disease.

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Innate immunity plays a prominent role in many renal diseases. In teleost fish such as the sea lamprey and the rainbow trout, the anterior kidney functions as a secondary lymphoid organ.[1] In mammalian species, functional evolution of the kidney has developed in a different direction: sorting of cells, proteins, electrolytes, and fluids. Remnants of our common vertebrate evolutionary past, however, are still present in human kidneys, as a multitude of proinflammatory genes can be activated in renal parenchyma.

Renal cells are capable of expressing Toll-like receptors[2] with subsequent activation of mitogen-activated protein kinases, nuclear factor-κB, and activator protein-1 (Figure 1). Pathogen recognition receptors such as the Toll-like receptors expressed by renal epithelial cells contribute not only to the exacerbation of infection-mediated renal disease, but also to the self-perpetuation of lupus nephritis by recognition of nucleosomal autoantigens. Renal cells are also reported to express receptors for complement components.[3] Upon activation by proinflammatory cytokines such as interleukin-1β or interleukin-2, renal cells have been reported to express receptors for C3a, C3b, and C1q, resulting in the attraction, adhesion, and activation of inflammatory cells. Furthermore, renal cells have been shown to express costimulation molecules for T-cell activation.[4] These transmembrane proteins are required for effective activation of the CD3–T-cell receptor complex on both cytotoxic and helper T cells. Expression of B7 isoforms (CD80/86), inducible T-cell co-stimulator ligand, and CD40 has been described on renal epithelial cells, on mesangial cells, and on glomerular endothelial cells, with a profound impact on the course of transplant rejection. The above-mentioned multitude of outside-in signaling by these receptors on epithelial cells results in the production of a variety of inflammatory cytokines and chemokines,[5] which attract inflammatory cells and subsequently amplify the inflammatory response in the kidney. Last but not least, both inflammation-activated and CD40L-activated renal cells have been demonstrated to produce complement components such as C3 (ref. 6), which seem more important in the course of renal disease than systemic production by the liver, as shown by elegant kidney transplantation experiments in C3-deficient mice by Pratt *et al.*[7]

With these factors, renal cells actively participate in the inflammatory response rather than responding to it. The propensity of renal cells to participate in immune responses is one of the limitations encountered in kidney transplantation, in which human leukocyte antigen matching and prevention of ischemic injury are crucial for graft outcome.

The study by Mrug *et al.*[8] (this issue) shows that innate immunity is also involved in the progression of polycystic kidney disease (PKD). Genome-wide expression analysis was performed in *cpk* mice, carrying a genetic mutation in the gene encoding the cilia-associated protein cystin, a model for recessive polycystic disease. In severely as compared with mildly affected animals, preferential upregulation was found of genes expressed by type II activated macrophages. In addition, increased levels of complement component C3 were found both in cyst-lining and in non-cystic epithelia. It seems unlikely that the involvement of innate immunity remains confined to the recessive form of polycystic disease. Both recessive

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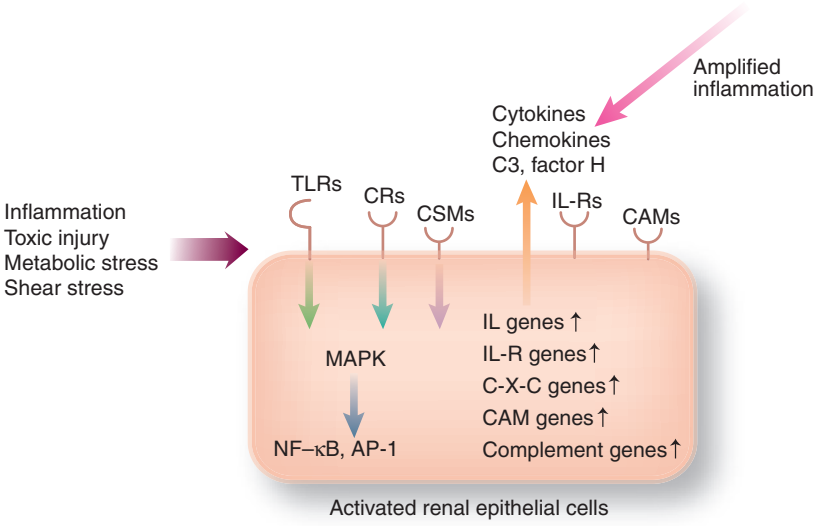

Figure 1 | Innate immunity and renal cells. AP-1, activator protein-1; CAM, cellular adhesion molecule; CRs, complement receptors; CSMs, co-stimulation molecules; IL, interleukin; IL-R, interleukin receptor; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-κB; TLR, Toll-like receptor.

and dominant PKD is accompanied by tubulointerstitial fibrosis and extensive infiltration by inflammatory cells, leading to deterioration of renal function in autosomal dominant PKD (ADPKD), and activation of mitogen-activated protein kinases and activator protein-1 have been demonstrated in cystic kidneys from patients with ADPKD and in a corresponding mouse model.[9] Expression profiling for a limited set of genes in patients with ADPKD shows increased expression of immune response genes in addition to genes associated with epithelial–mesenchymal transition and genes involved in extracellular matrix turnover.[10] The study of Mrug *et al.*[8] underlines the involvement of innate immunity in a final common pathway of progressive renal disease, which is independent of the underlying etiology. It also provides an opportunity for more selective therapeutic interventions aimed at innate immunity control by targeting for signaling pathways that result from activation of innate immunity receptors on renal cells. Interference with innate immunity has the advantage of controlling both the inflammatory response by the immune system and the responding renal cells. However, interference with innate immunity has the risk of inactivation of our first line of defense against bacterial and viral infections.

Future perspectives in human renal disease will require carefully designed treatment protocols after rigorous preselection by *in vitro* systems and experimental models.

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